Long-term suppression of hepatitis B virus replication by short hairpin RNA expression using the scaffold/matrix attachment region-based replicating vector system pEPI-1.

Abstract:
Since the emergence of viral resistance of hepatitis B virus (HBV) during treatment is becoming an important issue even with newer drugs, there is a need for alternative treatment options such as, for example, RNA interference (RNAi) technology. While short-term suppression of HBV replication is easily achieved with small interfering RNA oligonucleotides, this is not the case for long-term suppression due to the lack of an optimal vector system. Based on the nonviral scaffold/matrix attachment region (S/MAR)-based vector system pEPI-1, which is free of common side effects and is stably retained as an episome even in the absence of selection, we designed a short hairpin RNA (shRNA) expression vector called pEPI-RNAi for HBV suppression. HBV-replicating HepG2.2.15 cells were transfected with pEPI-RNAi, and the intracellular status of the plasmid was followed by PCR and Southern analysis. HBV replication was measured on the DNA, RNA, and protein level. HBV RNA expression was reduced by almost 85% 3 months posttransfection with pEPI-RNAi. At 8 months posttransfection in the absence of antibiotic selection pressure, the suppression level was still 70% and the vector was retained as an episome. The reduction of total intracellular HBV DNA at this point was 77%, showing a marked suppression of HBV DNA replication.
At a comparable level, secretion of viral antigens, as well as progeny HBV virions, was inhibited. The S/MAR-based vector system pEPI-1 allows long-term suppression of HBV replication by the expression of suitable shRNAs. Due to its unique properties compared to commonly used vectors, it provides an interesting option for the treatment of chronically HBV-infected individuals.

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